UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/384,811	08/27/1999	PEGGY LEMAUX	18941000710U	8311

20350 7590 06/16/2004

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
COLLINS, CYNTHIA E	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/384,811	LEMAUX ET AL.	
	Examiner	Art Unit	
	Cynthia Collins	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *April 8, 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,11-16 and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,11-16 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed April 8, 2004, in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on March 8, 2004 (after-final amendment) and May 7, 2004 (preliminary amendment) have been entered.

Claims 1-8, 10 and 17-25 are cancelled.

Claim 9 is currently amended.

Claim 26 is newly added.

Claims 9, 11-16 and 26 are pending and are examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9, 11 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods that require the introduction of both a Ds element comprising a transgene and a nucleic acid sequence encoding an Ac transposase

into a barley plant population, whereby the Ds element comprising the transgene reintegrates into a barley plant genome through transposase-mediated excision, does not reasonably provide enablement for methods that require the introduction of only a Ds element comprising a transgene into a barley plant population, whereby the Ds element comprising the transgene reintegrates into a barley plant genome through transposase-mediated excision. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to a method of generating a stably transformed barley plant comprising a stably expressed transgene, the method comprising introducing the Ds element comprising the transgene into a barley plant population, whereby the Ds element comprising the transgene reintegrates into a barley plant genome through transposase-mediated excision; and selecting a barley plant in which the Ds element comprising the transgene is reintegrated, generating at least two generations of progeny in which the transgene is expressed, thereby obtaining the stably transformed barley plant comprising the stably expressed transgene.

The specification discloses a method of generating a stably transformed barley plant comprising a stably expressed transgene, the method comprising introducing the Ds element comprising the transgene into a barley plant, and crossing said barley plant with another barley plant comprising an Ac element to produce offspring that comprise both the Ds element comprising the transgene and the Ac element, whereby the Ds element comprising the transgene reintegrates into the offspring's genome through transposase-mediated excision; and selecting a barley plant in which the Ds element comprising the

transgene is reintegrated, generating at least two generations of progeny in which the transgene is expressed, thereby obtaining the stably transformed barley plant comprising the stably expressed transgene. (pages 22-26 Example 3) The specification does not disclose any method in which only a Ds element comprising a transgene is introduced into a barley plant population, whereby the Ds element comprising the transgene reintegrates into a barley plant genome through transposase-mediated excision.

The full scope of the claimed invention is not enabled because Applicant has not provided guidance with respect to how to introduce only a Ds element comprising a transgene into a barley plant in a manner that would allow for the Ds element comprising the transgene to reintegrate into the plant's genome through transposase-mediated excision. Such guidance is necessary because transposase-mediated excision of a Ds element specifically requires the activity of an Ac transposase, which transposase activity is not endogenous to barley.

The specification, referring to the prior art, describes Ac and Ds elements at page 6 lines 21 through page 7 line 16, where it is disclosed that the Ac/Ds transposable element system is endogenous to maize, and that the non-autonomous Ds elements, which carry internal deletions, can only transpose when the Ac transposase is provided in trans. The specification additionally explains, at page 2 lines 8-10, that non-autonomous elements from one transposable element family (in this case Ds) can be transactivated only by the autonomous member of the same family (in this case Ac). Accordingly, transposase- mediated excision of a transgene contained within a Ds element would not be expected to occur in barley absent the further introduction of a nucleic acid sequence encoding an Ac transposase, since barley does not contain such nucleic acid sequences

endogenously, and since transposase-mediated excision of a Ds element specifically requires the activity of an Ac transposase. Absent guidance with respect to how to introduce only a Ds element comprising a transgene into a barley plant in a manner that would allow for the Ds element comprising the transgene to reintegrate into the plant's genome through transposase-mediated excision, one skilled in the art would not know how to select a barley plant in which the Ds element comprising the transgene is reintegrated, which step is required to practice the claimed method.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 9 recites the limitation "the Ds element" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

Claims 9 and 11-14 remain rejected, and claim 26 is rejected, under 35 U.S.C. 103(a) as being unpatentable over McElroy et al. (The Plant Journal, 1997, Vol. 11, No. 1, pages 157-165) in view of Wan et al. (Plant Physiol., 1994, Vol. 104, pages 37-48) and Bancroft et al. (Mol. Gen. Genet., 1992, Vol. 233, 449-461), further in view of Ritala et al., (Plant Molecular Biology, 1994, Vol. 24, pages 317-325), Funatsuki et al., (Theor. Appl. Genet., 1995, Vol. 91, pages 707-712), Koprek et al., (Plant Science, 1996, Vol. 119, pages 79-91), Brinch-Pedersen et al., (Plant Molecular Biology, 1996, Vol. 32,

pages 611-620), and Jensen et al., (Proc. Natl. Acad. Sci. USA, 1996, Vol. 93, pages 3487-3491), for the reasons of record set forth in the office action mailed November 5, 2003.

Claims 15-16 remain rejected under 35 U.S.C. 103(a) as being unpatentable over McElroy et al. (The Plant Journal, 1997, Vol. 11, No. 1, pages 157-165) in view of Wan et al. (Plant Physiol., 1994, Vol. 104, pages 37-48) and Bancroft et al. (Mol. Gen. Genet., 1992, Vol. 233, 449-461), further in view of Ritala et al., (Plant Molecular Biology, 1994, Vol. 24, pages 317-325), Funatsuki et al., (Theor. Appl. Genet., 1995, Vol. 91, pages 707-712), Koprek et al., (Plant Science, 1996, Vol. 119, pages 79-91), Brinch-Pedersen et al., (Plant Molecular Biology, 1996, Vol. 32, pages 611-620), and Jensen et al., (Proc. Natl. Acad. Sci. USA, 1996, Vol. 93, pages 3487-3491), and further in view of Perera et al. (Plant Molecular Biology, 1993, Vol. 23, pages 793-799), for the reasons of record set forth in the office action mailed November 5, 2003.

Applicants' arguments filed March 8, 2004 have been fully considered but they are not persuasive.

Applicants argue as in previous responses that the Examiner has not established a proper case prima facie obviousness, which requires that the prior art suggest all of the elements of the claimed invention, that there is a motivation to combine the reference teachings, and that there is a reasonable expectation of success at arriving at the claimed invention. Applicants respectfully maintain that at the time of the invention, one of skill in the art had no motivation to use the Ac/Ds system in barley because of the high degree of methylation in the barley genome. Applicants also maintain moreover that even if one

were to try to use the system in barley, there was no reasonable expectation of success. As explained by Dr. Lemaux in her Declaration (submitted with the response of December 3, 2002) because of methylation and gene silencing in the barley genome, it could not reasonably be expected that the Ac/Ds system could generate transformants in which the transposable element can be reactivated and reinserted into the genome nor that the transgene would be expressed. (reply page 4)

The Examiner maintains as in previous actions that the prior art suggests all of the elements of the claimed invention, as the prior art teaches barley transformation (Wan et al.), including stable barley transformation with multiple types of hetereologous genes (Ritala et al., Funatsuki et al., Koprek et al., Brinch-Pedersen et al., and Jensen et al.) and further including stable transgene expression through at least two generations of barley progeny (Ritala et al., page 323 second column last paragraph, and Jensen et al., page 3490 first column lines 15-22), Ac transposase-mediated excision of the Ds element to generate a functional Gus gene in transiently transformed barley scutellar cells (McElroy et al.), the use of Ac/Ds in other heterologous systems (Bancroft et al.), and the use of *cod A* as a negative selectable marker for transformed plants (Perera et al.). The Examiner also maintains as in previous actions that that there is both a motivation to combine the reference and a reasonable expectation of success, as the prior art teaches how transposable elements may be used in heterologous systems, as well as that stable transformation of barley with stable transgene expression through at least two generations can be achieved, and that Ac transposase-mediated excision of Ds can successfully occur in barley cells.

Applicants assert that they here provide evidence that there was a long-felt need for transformation methods that avoid the problems of gene inactivation, particularly in cereals, such as barley. Applicants assert that the present invention is surprisingly effective as a means for producing transgenic barley plants that stably express transgenes through multiple generations, and point out that it is well established that evidence that an invention provides a solution to a long-felt need in the art can be used to rebut a prima facie case of obviousness. Applicants further point out that an applicant can also present evidence of the surprising effectiveness of the invention to rebut a prima facie case. (reply pages 4-5)

Applicants point in particular to the attached Declaration by Dr. Peggy Lemaux and the publication by the present inventors (Koprek et al., Plant Physiol. 125:1354-1362 (2001)) as providing evidence that prior art gene delivery methods have been plagued by problems of gene inactivation. Applicants point out that the Declaration and reference also show that transposase-mediated gene delivery in barley, as claimed here, is surprisingly effective in producing transgenic barley plants with stable transgene expression through generation advance, and that in particular, as compared to prior art methods, such as biolistics, electroporation and Agrobacterium-mediated gene delivery, methods of the present invention result in a greater percentage of single copy insertions, which are much less prone to gene silencing. Applicants point out that unlike prior art methods, transposons preferentially insert in transcriptionally active regions of the barley genome, which further limits the degree of transgene silencing. (reply page 5)

Applicants point in particular to the Declaration where Dr. Lemaux notes that gene inactivation has been observed in many transgenic plants and has been especially

problematic in cereals. Applicants point out that biolistics, the most commonly used method of transformation, leads to complex, multicopy transgene integration, that results in gene silencing in more than 50% of transgenic plants (see, Lemaux Declaration, ¶5 and Koprek et al., page 1354, first column). Applicants maintain that since the successful use of transgenic plants in agriculture requires the development of plants that stably express the transgene during generation advance, there is much interest in developing methods that overcome these problems. Applicants assert that as of the time Koprek et al. was filed, as well as the filing of the present application, these problems had not yet been solved. Applicants point out that their methods provide an unusually high percentage of transformants with single copy insertions integrated in transciptionally active regions that avoid the problems of gene silencing and thus lead to stable transgene expression (see, Lemaux Declaration, ¶6 and Koprek et al. page 1355, first column). (reply pages 5-6)

The Examiner maintains that Applicants' arguments with respect to the problems of gene inactivation (transgene silencing) are not germane to the instant rejection, as the rejected claims are not directed to a method which addresses the problems of gene inactivation. The Examiner also maintains that Applicants' arguments with respect to the production of a greater percentage of single copy insertions and preferential insertion in transcriptionally active regions of the barley genome are not germane to the instant rejection, as the rejected claims are not directed to a method which addresses specific problems of gene inactivation by producing a greater percentage of single copy insertions and/or by resulting in preferential insertion in transcriptionally active regions of the barley genome. The Examiner additionally maintains that Applicants' arguments with respect to producing transgenic barley plants that stably express transgenes through

multiple generations are not germane to the instant rejection, as the cited prior art teaches the production of barley plants that stably express transgenes through multiple generations (Ritala et al., page 323 second column last paragraph, and Jensen et al., page 3490 first column lines 15-22).

Applicants also point in particular to ¶7 of the Lemaux Declaration describing the production of barley plants using the claimed method, and to the Table 1 on page 1356 of Koprek et al., which shows the results of the analysis of TNP plants (in which the Ds element carrying a bar selectable marker gene had transposed and segregated away from the Ac transposase gene) and nTNP plants (which lack transposase genes and in which the Ds element carrying a bar selectable marker gene is still at the original site of integration) for stable transgene expression through the F4 generation. Applicants point out that the percentage of TNP lines exhibiting transgene silencing across generations was much lower than the percentage of nTNP lines. (see also Lemaux Declaration, ¶8). Applicants further point out that comparing only barley plants comprising a single copy of the transgene showed even more stability of transgene expression in TNP plants relative to nTNP plants (Lemaux Declaration, ¶9 and Table 1 and Figure 2 of Koprek et al.) (reply pages 6-7)

Applicants maintain that their experiments show that transposase-mediated excision and reinsertion dramatically increases the stability of transgene expression from genes embedded in the Ds element in barley plants (Lemaux Declaration, ¶10). Applicants further point to the fact that the Ds elements in these plants had integrated in single to low copy regions of the genome (i.e. transcriptionally active regions of the

genome), to the authors' statement that this factor that may play a decisive role in the unusual stability of the transgenes in these plants, and to the authors' conclusion that that the use of transposable elements in gene delivery "leads to large numbers of independent single-copy transgenic plants." (Lemaux Declaration, ¶11; Figure 3 and discussed in the second column of page 1356 of Koprek et al.; Koprek et al. page 1359, second column; Koprek et al. page 1360, first column). (reply page 7)

The Examiner maintains that Applicants' observation that the percentage of TNP lines exhibiting transgene silencing across generations was much lower than the percentage of nTNP lines is not germane to the instant rejection, as the rejected claims are not directed to a method for reducing transgene silencing in a population of plants, or to methods that produce a population of plants that exhibit a lower percentage of transgene silencing as compared to plants prepared by other methods. The Examiner also maintains that the rejected claims are not directed to a method that dramatically increases the stability of transgene expression from genes embedded in the Ds element in barley plants after transposase-mediated excision and reinsertion as compared to before transposase-mediated excision. The Examiner further maintains that the rejected claims are not directed to a method for producing higher numbers of independent single-copy transgenic plants, or to methods that produce higher numbers of independent single-copy transgenic plants as compared to other methods.

Applicants argue in conclusion that the methods of the present invention address a long-felt need for efficient methods for producing transgenic barley plants that stably express an introduced transgene, and that the data discussed above properly rebut a prima

facie case of obviousness by showing that the methods of the invention address this need by their surprising effectiveness in producing such plants (reply pages 7-8).

The Examiner maintains that the methods as currently claimed do not address a long-felt need for efficient methods for producing transgenic barley plants that stably express an introduced transgene, because the currently rejected claims impose no requirement for efficiency, and because the currently rejected claims recite no limitations that clearly distinguish Applicants' method from what is disclosed in the prior art. The Examiner further maintains that that the data discussed above do not rebut the prima facie case of obviousness, because the data are directed to issues that the currently rejected claims do not address.

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia Collins whose telephone number is (571) 272-0794. The examiner can normally be reached on Monday-Friday 8:45 AM -5:15 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Cynthia Collins

AMY J. NELSON, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600